Rare Diseases Clinical Development at CDER

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Outline

- New Rare Diseases Program at CDER
- Orphan drug history at FDA
- Clinical development of treatments for rare diseases
- What the Rare Diseases Program is doing
  - What we've heard from you
  - How can we help
  - Where to go for help

FAQ: What is considered a “rare disease”?

- Rare disease = Orphan drug definition
  - a disease or condition affecting <200,000 people in the United States

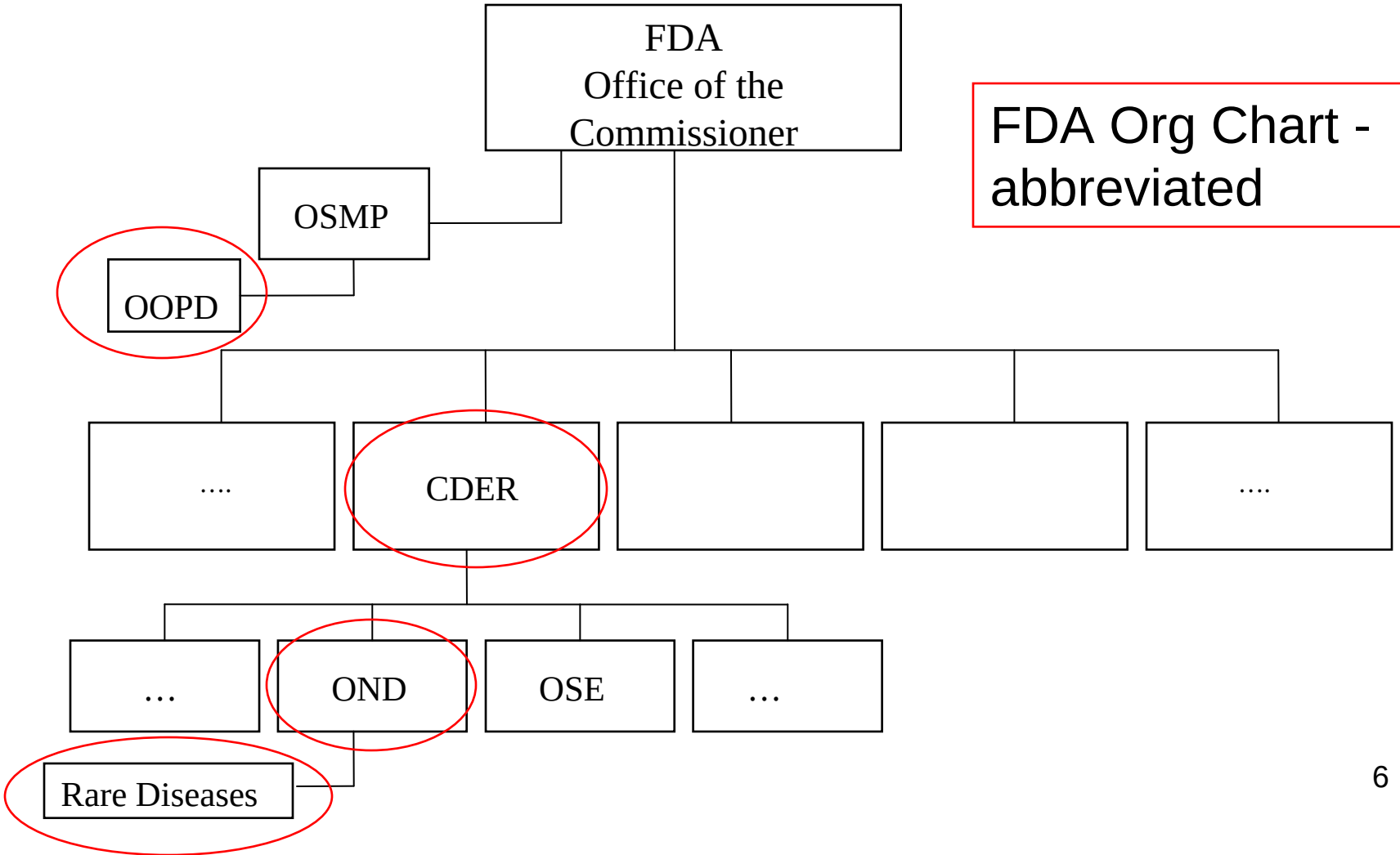
Rare Disease Program in CDER

- Being established in CDER OND as of February 2010
  - Located in the Office of New Drugs
    - Associate Director for Rare Diseases (ADRD)
    - RD Regulatory Project Manager – Larry Bauer, RN
    - Report to Director of the Office of New Drugs – Dr. Jenkins

Rare Diseases Program

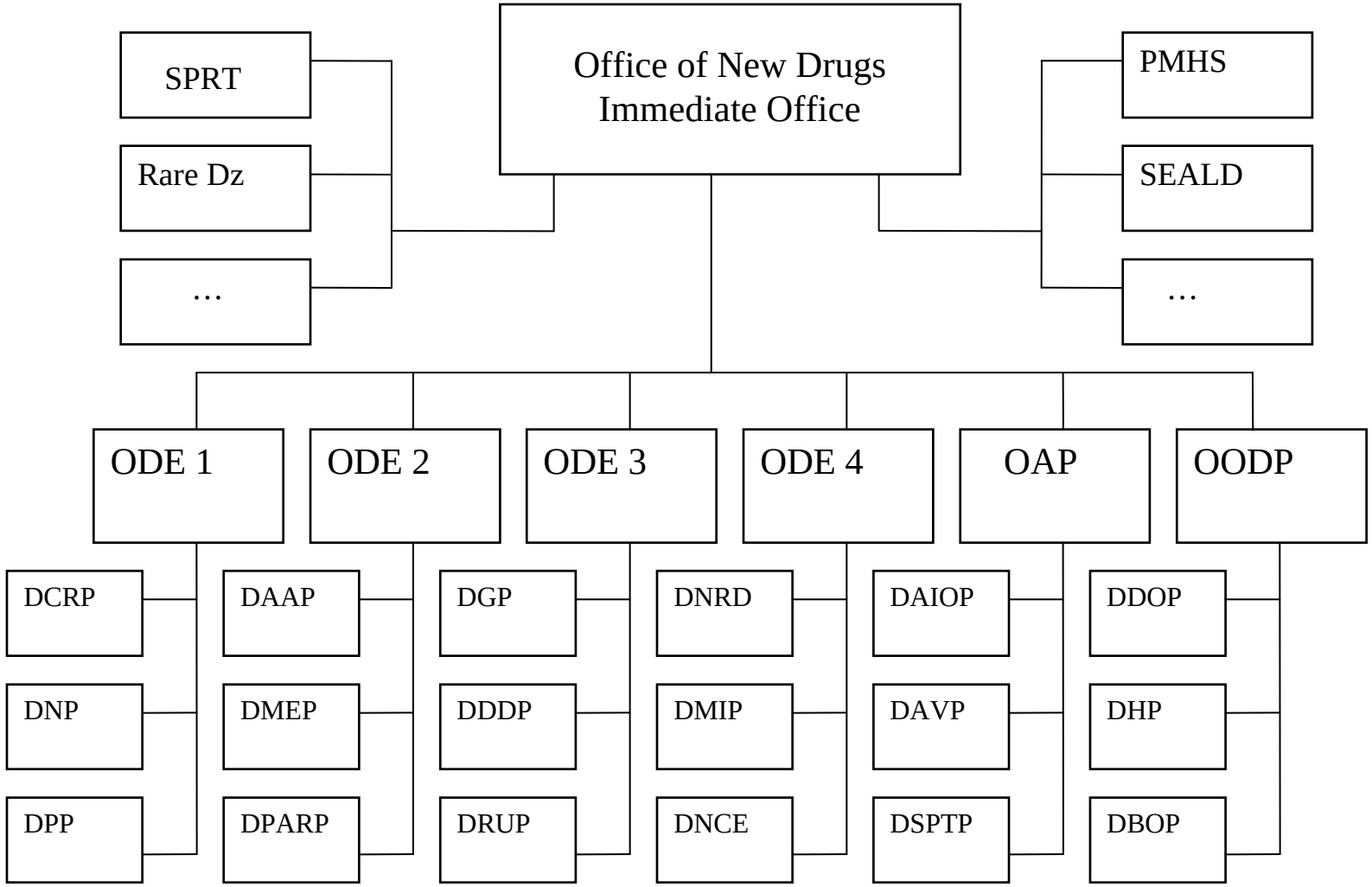
- Goal: To facilitate and support the research, development, regulation and approval of drug and biological products for the treatment of rare disorders
  - Complement the work of FDA's Office of Orphan Product Development (OOPD)
  - CDER's focal point of contact for Rare Disease stakeholders
    - Facilitate interactions with CDER
    - Help navigate complex regulatory requirements

FAQ #2: OOPD and OND Rare Disease Program



FDA Org Chart - abbreviated

OND Org Chart (abbrev.)



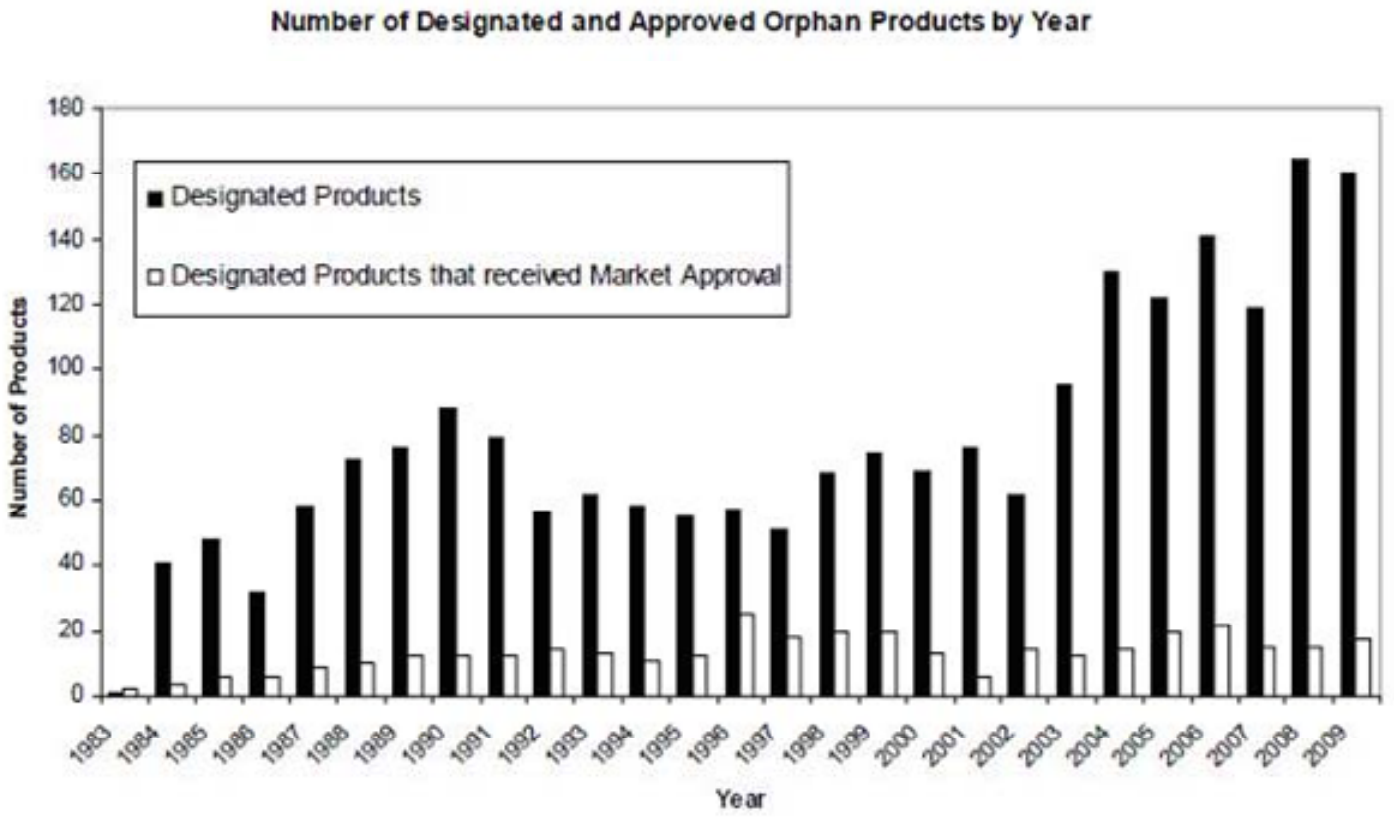
Rare Disease History at FDA

- Orphan Drug Act (ODA)
  - Signed into law in 1983
  - Purpose
    - To promote the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases
  - Orphan Designation – Requirements:
    - Disease/condition with a prevalence <200,000 Americans
    - Adequate demonstration of a medical plausibility for the drug's expected benefit
  - Mainly provides financial incentives
    - Exempt from PDUFA fees (>$1 million)
    - 50% tax credit for clinical study costs
    - Eligible to apply for FDA Orphan grants program to support clinical research
    - 7 years marketing exclusivity for approved Orphan product

ODA cont.

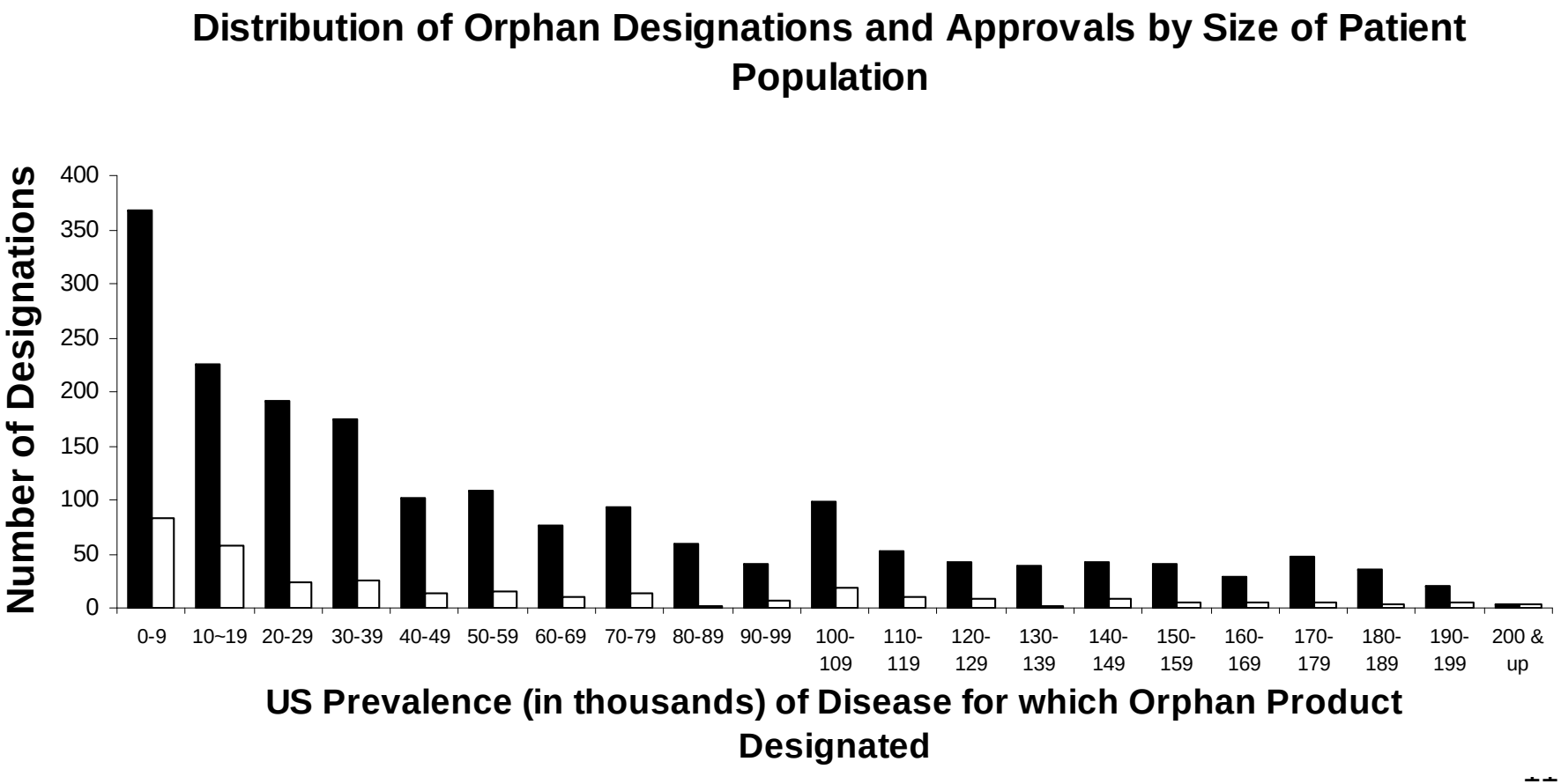
- Successful history:
  - In ~10 years prior to passage of ODA ~10 approved Orphan drugs
  - As of September 25, 2010 → 360 approved drug and biologic Orphan products
    - ~1/3 of all NME approvals are Orphan products
    - 2/3 of therapeutic biologic product approvals in 2008 & 2009 were Orphans
  - >2200 Orphan designations
    - Designations are increasing
    - ~25% of designations go on to receive marketing approvals

Orphan designations and approvals 1983-2009[1]



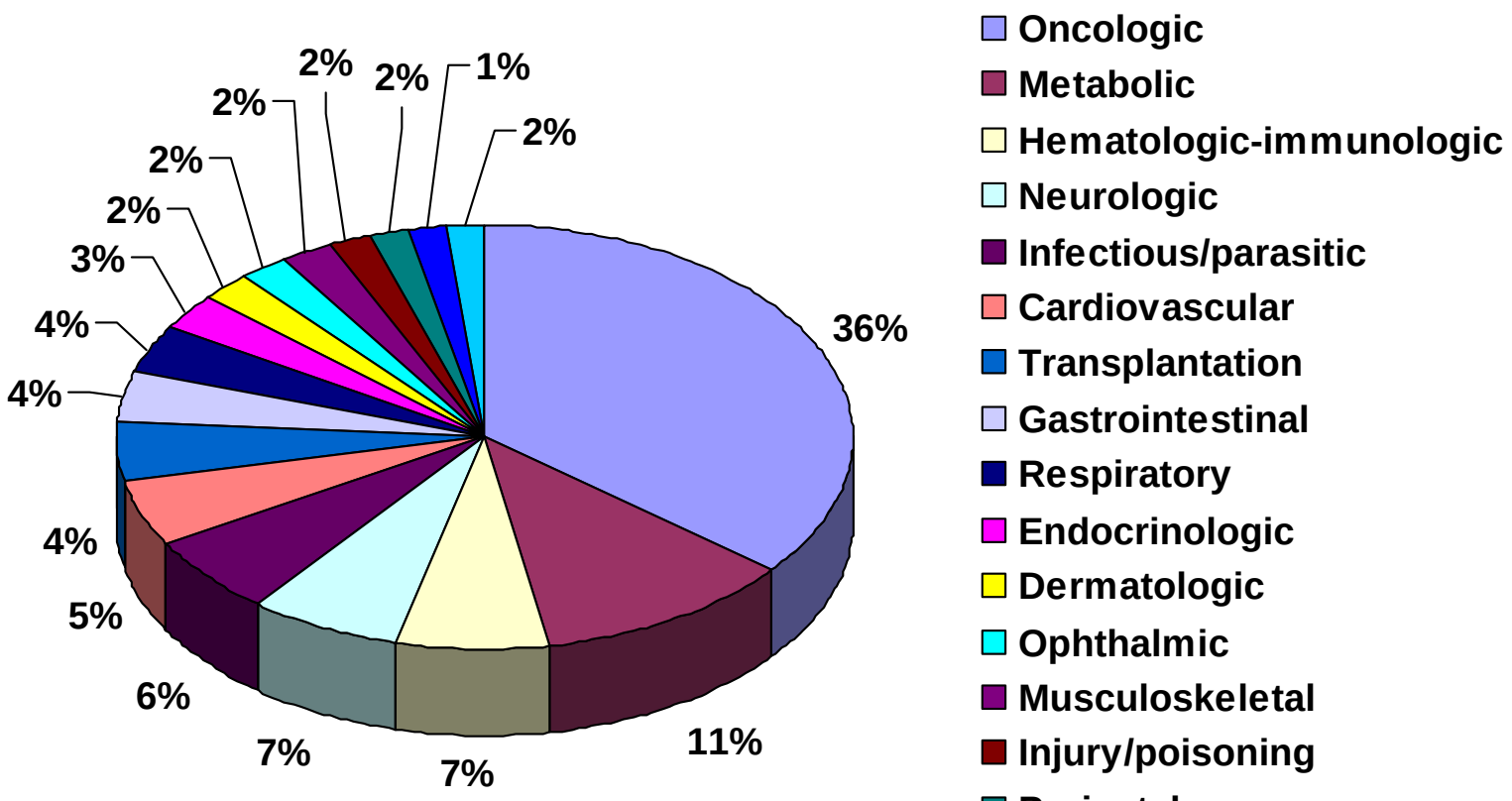
[1] Karst, KR. "Another Banner Year for Orphan Drug Designations". Hyman, Phelps and McNamara Law Blog. <http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/01/2009-another-banner-year-for-orphan-drug-designations-.html> <"Orphan Designations 2009">. <April 25, 2010>. January 21, 2010.

Population sizes for Orphan designated products[2]



[2]From: Cote, T. Presentation to FDA Rare Disease Review Ctte. March 11, 2010

Diseases/Conditions Targeted by Designated Orphan Drugs[3,4]



[3]2000-2006 Data

[4]From: Cote, T. Presentation to FDA Rare Disease Review Ctte. March 11, 2010

Orphan Designations and OND

- In the Office of New Drugs at CDER:
  1. Divisions of Drug and Biologic Oncology Products (~1/3)
  2. Division of Neurology
  3. Division of Hematology
  4. Division of Gastroenterology Products
     a. Inborn errors of metabolism
     b. GI products

- All OND Divisions receive and review rare disease applications

CDER NME Approvals 2008 & 2009

CDER New Molecular Entity Approvals

2008	**All #**	**Orphans #**	**% of all NMEs**
Drugs	21	6	29%
Biologics	3	2	67%
2009			
Drugs	19	4	21%
Biologics	6	4	67%

- So far in 2010 (September 25, 2010)
  - 17 NMEs approved (10 drugs, 7 biologics*)
  - **40% are Orphans** (3 drugs, 4 biologics*)

*One biologic AP under an NDA

Other Legislation

- For new drugs for serious or life-threatening conditions:
  - FDA Modernization Act of 1997 (FDAMA)
    - Called for amendments to Federal Food, Drug, and Cosmetic Act, some of which included:
      - Fast Track and Accelerated Approval
      - Priority review
      - Other
        - » Pediatric labeling requirements and exclusivity incentives
        - » ClinicalTrials.gov
  - Fast Track Designation
    - Combination of a drug product intended to treat serious/life-threatening condition ***and*** a claim that addresses an unmet medical need
    - Scheduled meetings
    - Rolling review

FDAMA cont.

- Accelerated Approval
  - Approval based on surrogate endpoint
    - Surrogate=reasonably likely to predict clinical benefit
    - Usually requires post-marketing studies to verify and describe clinical benefit
    - Subpart H - drugs (21 CFR 314.500)
    - Subpart E – biologics (§601.40)
- Priority Review
  - 6-month NDA/BLA PDUFA goal date instead of usual 10-mo
  - Determination made by review division at time of NDA/BLA submission

Challenges remain…

- Needs far outnumber available therapies
  - ~6000 rare diseases affecting ~25 million Americans[5]
  - Only ~200 of these diseases have an approved therapy
    - Off-label use of drugs is common for rare diseases

[5]Cote T, Kelkar A, Xu, K et al. Orphan products: An emerging trend in drug approvals. *Nature Rev. Drug Discov.* 2010;9(1):84.

Clinical Development Challenges

- Tend to be difficult diseases to study in clinical trials
  - Populations are small
  - Often chronic, progressive, serious, life-limiting and life-threatening with unmet medical needs
  - Highly diverse group of disorders
  - Natural history often not well (or incompletely) understood
  - Endpoints, outcome measures, tools, instruments, biomarkers usually lacking

Regulatory Approval Standard

- Orphan drugs are held to the same statutory requirements for demonstrating effectiveness and safety
- Orphan drugs must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Substantial evidence of benefit requires:
    - *Adequate and well-controlled clinical study(ies) (§314.126)*

Substantial Evidence of Effectiveness

- Adequate and well-controlled study:
  - Study has been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation" (§314.126)
- Clinical benefit:
  - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression

FDA's role

- Clinical trials in US conducted under Investigational New Drug Applications (INDs)
- FDA oversees clinical trials to help assure:
  - Subject safety
  - Interpretability of study results
  - Compliance with established regulations

Drug Development: Objectives

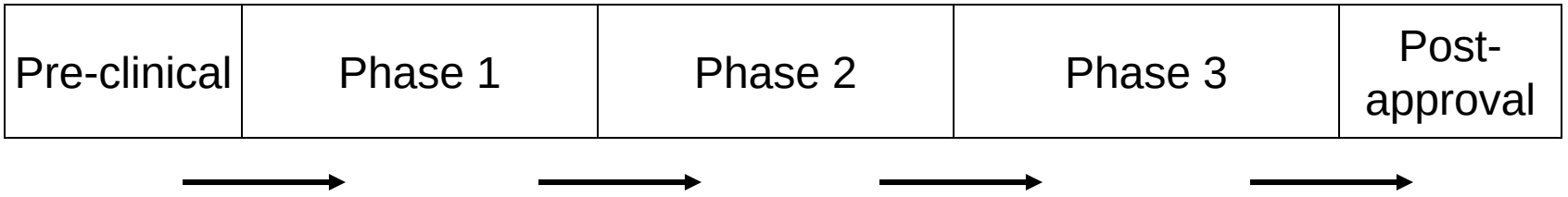
- Overall objectives for all drugs (Orphan and non-Orphan) - to determine that:
  - Drug is safe and effective for its proposed use
    - Benefits outweigh the risks
  - Drug's proposed labeling is appropriate to allow for its intended use
  - Methods used in manufacturing are adequate to preserve the drugs identity, strength, quality and purity
- That is, development program should tell the drug's whole story

Clinical Drug Development

- Development and testing demands high standards, scientific rigor and safety monitoring
- Rights and safety of research subjects must be protected
- Primary goal of a clinical trial is to establish cause and effect
  - Isolate the effect of a treatment and rule out factors that could lead to misleading findings (bias)
  - Establish a favorable risk-benefit profile for a new drug

IND Studies - Overview

- Generally stepwise, and generally divided into 3 phases:



- Step-wise series of events, each step building on the results of previous studies
  - Can't answer all the questions about a drug in one study - sequential, phased study is needed
- Studies usually get more complex as move from step to step

"Flexibility"

- Regulations provide room for flexibility in reviewing treatments for rare diseases
  - There are "many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards"
  - "…FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."

(§314.105)

Adequate and well-controlled

- Must incorporate generally accepted scientific principles for clinical trials
  - Clear statement of purpose
  - Permits a valid comparison with a control
    - Concurrent: placebo, no-treatment, active, dose-comparison
    - Historical
  - Method of selection of subjects
  - Method of assigning patients to treatment/control groups
  - Adequate measures to minimize bias
  - Methods of assessment of response are well-defined and reliable
  - Analysis of the results is adequate to assess the effects of the drugs

Substantial evidence (2)

- What constitutes substantial evidence of effectiveness?
  - Typically two adequate and well-controlled studies
    - *Independent substantiation* of experimental results – single clinical experiment not usually considered adequate scientific support for conclusion of effectiveness
  - At times, one study will considered as adequate
    - Defined in Guidance “Providing clinical evidence of effectiveness for human drug and biological products”

CDER Orphan Highlights of 2010

CDER Orphan approvals in 2010 (as of Sept 22, 2010):

Product	Indication	AP Month 2010	Division	NDA/BLA
Dalfampridine (Ampyra™, Acorda)	Improve walking in Multiple Sclerosis	January	DNP	NDA
Collagenase (Xiaflex™, Auxilium)	Dupuytren's contracture	February	DPARP	BLA
Velaglucerase (VPRIV™, Shire HGT)	Gaucher disease	February	DGP	NDA
Carglumic acid (Carbaglu®, Orphan Europe)	NAGS deficiency (UCD)	March	DGP	NDA
Alglucosidase alfa (Lumizyme®, Genzyme)	Late-onset Pompe disease	May	DGP	BLA
Glycopyrrulate (Cuvposa™, Shionogi)	Drooling in children with neurologic disorders (e.g., cerebral palsy)	July	DNP	NDA
Pegloticase (Krystexxa™, Savient Pharma)	Chronic gout not responsive to conventional therapy	September	DPARP	BLA

Approval history

- Dalfampridine (improve walking in Multiple Sclerosis)
  - 2 R, DB, PC trials, n=540
- Collagenase (Dupuytren's contracture)
  - 2 R, DB, PC trials, n = 374
- Velaglucerase (Gaucher disease):
  - One pivotal study → R, DB, parallel dose-group, n =25
  - Total program → 3 studies, n=99
- Alglucosidase alfa (late-onset Pompe disease):
  - One R, DB, PC trial, n=90
  - Additional supportive information from related experience in infantile-onset Pompe disease from a post-marketing registry, n=15
- Carglumic acid (NAGS deficiency):
  - OL, historically-controlled, retrospective case series, n=23
- Glycopyrrolate (drooling in children with neurological disorders)
  - One pivotal study → R, DB, PC, parallel, 8-week study, n=38
  - Total program → 2 studies, n=151
- Pegloticase (chronic gout in adult patients who do not respond to conventional therapy)
  - 2 R, DB, PC 6-month trials, n=212

Highlights (2)

- Diverse collection of diseases/populations studied
  - MS, Dupuytren's contracture, genetic disorders (3), gout, pediatric disorders, etc.
- Range of study designs
  - R, DB, PC
  - OL, historically-controlled
- Program sizes
  - Dalfampridine n=540
  - Carglumic acid n=23
- Scope of studies needed to provide sufficient evidence
  - E.g., single study – carglumic acid → step-wise programs for most others
  - Totality of evidence will be considered
- Endpoints accepted
  - Novel and established/well-described
  - Meaningful, interpretable, well-defined and reliable
  - "Fit for Purpose"

Key Points for Orphans

- No one right way to do things for rare diseases
  - Design considerations based on disease and drug/product characteristics, population under study, etc.
  - Still need to demonstrate “substantial evidence of effectiveness”
    - Flexibility in how that is achieved
    - Multiple pathways defined in existing guidance
      - E.g., single study with:
      - Pharmacologic/pathophysiologic endpoints
      - Multiple endpoints, different events (measures)
      - Statistically persuasive findings

Key Points (2)

- Safety is always an important concern for drug development throughout the entire drug development process
  - First-in-human (or first-in-disease) IND studies
    - Primary objective in early phase (Phase 1) is safety
    - Preclinical information (e.g., animal toxicology) is necessary
      - To assure that it is reasonably safe to conduct the proposed clinical investigation(s) [§312.23(a)(8)]
      - Consider initial human population to be studied
        - » normal volunteers
        - » Serious/life-threatening diseases

Key Points (3)

- IND submissions (as with non-rare diseases) (§312.23)
  - General investigational plan
  - Protocol
  - Investigator Brochure
  - CMC, animal toxicology, previous human experience, and other information, as applicable
- At each stage of development, FDA will focus on:
  - Assuring safety and rights of subjects participating
  - Scientific quality of the clinical investigations
  - Likelihood that the investigation will yield data capable of meeting statutory standards for marketing approval

Key Points (4)

- Strong communication with FDA increases chances of a successful outcome
  - Meet early and often (formal meetings)
  - Encouraged by FDA to "aid in the evaluation of the drug and in the solution of scientific problems…" "Free, full, and open communication…" (§312.47)
  - Contact the Review Division
    - Consistent point of contact is the Regulatory Project Manager in the OND Review Division
  - Formal policies and procedures for meetings
    - Guidance document: "Formal meetings between the FDA and sponsors or applicants"[8]

Key Points (5)

- Much of work done before (pivotal) study starts
  - Map out clinical develop program as early as possible
  - Recommend doing a natural history study early on
  - Early phase trials very important to inform design pivotal trial(s) – even if very small
  - Areas for development
    - Endpoints and outcome measures
    - Translational science (e.g., biomarkers)
    - Animal studies, e.g., KO models of disease

Rare Diseases 2010 and beyond

- Goal of Rare Diseases Program:
  - Facilitate, support and accelerate the development of rare disease (RD) drug development and approvals
- Major areas of focus
  - Communication
  - Training
  - Scientific development
  - Regulatory science

How are we proceeding

- Communication and collaboration with rare diseases stakeholders, some examples:
  - National Organization for Rare Diseases (NORD)-FDA-NIH Task Force
  - NIH Therapeutics for Rare and Neglected Diseases (TRND) – FDA collaboration
  - NIH Office of Rare Diseases Research
  - Rare Disease Review Committee
    - Legislative mandate (Section 740, Brownback-Brown amendment)
    - Intra-FDA multi-center, multi-disciplinary committee
    - Parallel study commissioned by FDA and NIH from Institute of Medicine – report to be published early October 2010
  - Numerous advocacy and disease-oriented groups
    - E.g., CF Foundation, Muscular Dystrophy, Genetic Alliance, National Institute for Neurological Disorders and Stroke (NINDS)

Proceeding (2)

- Some general themes are emerging, some examples:
  - Requests for:
    - More clarity/transparency with regulatory process, decision making, consistency
    - More guidance on emerging science (e.g., biomarkers) and novel study designs (e.g., adaptive statistical designs), and for rare disease drug development
    - Recognition of need for better scientific foundation, e.g., natural history studies, biomarkers, outcome measures
    - More collaboration between all stakeholders

[7]National Organization for Rare Disorders, Inc. NORD Focus Groups on Orphan Product Development presented by Noah Pines. www.rarediseases.org/info/corporate_council_ppt_2010. May 2010.

In progress

- Training and Education
  - Inside and outside FDA
    - Accelerating Therapies for Rare Diseases Workshop
      - co-sponsored by FDA, NIH, NORD and Duke University Medical Center
      - October 18-20, 2010
      - First annual
    - Internal CDER training
      - February 2011
    - Future plans
      - Web-learning

In progress (2)

- Scientific Development
  - Numerous collaborations, some recent examples
    - Gaucher disease biomarkers (FDA, NGF)
    - Aerosolized antimicrobials for the treatment of CF (sponsored by CDER's Office of Anti-microbial Products)
    - Anti-sense oligonucleotides in neuromuscular disorders (NINDS, FDA, PPMD, MDA, CNMC)
    - Niemann-Pick type C (NINDS)
    - CNS manifestations of inborn errors of metabolism (FDA, NIH ORDR & NINDS)

In progress (3)

- Additional goals:
  - Regulatory Science
    - Refining policies and procedures Advice generation
      - Multi-disciplinary CDER work groups in progress
        - » E.g., Biostatistics, Pharmacotoxicology, Clinical
      - Exploration of additional areas in future
    - Study rare disease drug approval history and use this knowledge to move forward
  - Communication
    - Improved availability of relevant RD information on FDA website – coming soon
      - "One-stop shopping"

Where do I go for help?

- Where are you in development program?
  - Ready/almost ready for clinical trials
    - IND opened or to request pre-IND meeting → contact OND review division. Contact list:
      - www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM206032.pdf
    - Not sure who that is or not quite ready (but have some questions)
      - OND Rare Diseases Program, (Anne Pariser, Larry Bauer)
  - Any point in development, Orphan designations, Orphan grants
    - Office of Orphan Product Development
      - http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

OOPD and OND RDP

- OOPD
  - Administrates ODA
    - Designations
    - Exclusivity
    - Orphan grants
  - Device programs
    - Pediatrics
    - HUE, HDE
  - Strong advocacy work with RD stakeholders
- OND RDP
  - Facilitate communication within CDER/OND review divisions
  - Focus on complex regulatory requirements for INDs, NDAs and BLAs
  - Develop policy, procedures and advice for RD clinical development in CDER

Common areas: coordinate communication across FDA centers and offices, and with outside stakeholders; enhance RD information available on FDA website

Help (2)

- CDER Guidance page
  - Many Guidances available, many topics, not specific to rare diseases.
    - http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Help (3)

- Other FDA
  - Center for Biologics Evaluation and Research
    - http://www.fda.gov/BiologicsBloodVaccines/default.htm
    - Office of Blood Research and Review
      - E.g., coagulation factors, immunoglobulins
    - Office of Cellular, Tissue and Gene Therapies
    - Office of Vaccine Research and Review
  - Center for Devices and Radiological Health
    - Includes interventions and testing (e.g., newborn screening tests)
    - http://www.fda.gov/MedicalDevices/default.htm

Help (4)

- Outside FDA – who can help
  - Translational medicine, drug discovery
    - NIH TRND
      - www.rarediseases.info.nih.gov/TRND/
  - General help, research resource information
    - NIH Office of Rare Diseases Research
      - www.rarediseases.info.nih.gov/Default.aspx
    - National Organization for Rare Disorders
      - www.rarediseases.org
    - Genetic Alliance
      - www.geneticalliance.org
    - Disorder-specific advocacy groups
      - Many of these – listings on NORD and GA websites

In Conclusion

- Best access for patients to an effective therapy is an approved drug
- Successful clinical development of treatments for rare diseases possible and a growing area of research
- To improve chances of success of rare disease clinical development programs
  - Strong communication and collaboration are necessary
    - Recommend FDA involvement in planning as early as possible

Contact Information

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- Acknowledgement
  – Tim Cote, OOPD, FDA

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     - Office of Orphan Product Development
     http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm
     - Orphan Drug Act at:
     http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/OrphanDrugAct/default.htm
     - Code of Federal Regulations: (21CFR, Food and Drug Law)
     http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
       - IND regulations 312
       - NDA 314
       - Biological products 600

References (2)

2. Many Guidances available, many topics, not specific to rare diseases

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Some Guidances:

3. Formal meetings between the FDA and sponsors or applicants

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

4. Fast Track drug development programs – designation, development, and application review

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077104.pdf

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4. Content and format of investigational new drug applications (INDs) for Phase1 studies of drugs
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5. Providing clinical evidence of effectiveness for human drug and biological products
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf
6. E10 Choice of control group and related issues in clinical trials
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073139.pdf
7. Statistical principles for clinical trials
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf